

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA  
BENDIOCARB

Chemical Code # 001924, Tolerance # 50094  
SB 950 # 228

November 30, 1987  
Revised: 11/17/88, 8/4/89, 8/20/90, 4/3/97

I. DATA GAP STATUS

Combined. rat:	Data gap, inadequate study, possible adverse effect (Chronic) indicated
Chronic, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	Data gap, inadequate study, possible adverse effect indicated
Teratology, rat:	Data gap, inadequate studies, no adverse effect indicated
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

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Toxicology one-liners are attached.

All records through volume 076, record 089936, have been examined.

\*\*indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: T970403

Summary by Martz, November 30, 1987

Revised by Davis, 11/17/88; M. Silva, 8/4/89, 8/20/90; Gee, 4/3/97

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

### COMBINED, RAT

#### Subchronic Studies:

038 002286 "Ninety-Day Subacute Oral Toxicity - Rats," (Nor-Am Chemical Company). A summary paragraph only was provided (summary of 992142, so a worksheet was not done). The entire report was as follows: "Groups of 20 male and 20 female rats were given diet containing 0, 0.4, 2, 10, 50 or 250 ppm of bendiocarb for 90 days. Observations in all dose groups comprised clinical signs, mortality, bodyweight, food consumption, hematology, blood biochemistry, blood cholinesterase activity, urinalysis and gross postmortem and histopathological examinations. There was no overt sign of toxicity or histopathological change associated with treatment. Blood cholinesterase activity was reduced in males given 50 ppm and in both males and females receiving 250 ppm. The no effect level for depression of cholinesterase activity therefore was 10 ppm." (M. Silva, 7/11/90).

001 992142 "The Toxicology of NC 6897: 3-Month Dietary Toxicity Test on NC 6897 in the Rat," (Sanderson, D.M., FISON'S Ltd., Agrochemical Division, Essex, England, 2170). Bendiocarb (NC 6897 in 25% WP formulation CR 6862/2; made fresh each week; purity = 76%) Was fed, in diet, to Wistar rats at 0 (1% premix), 0.4, 2, 10, 50 and 250 ppm (20/sex/group) for 3 months. No adverse effect indicated. NOEL > 250 ppm (no significant effects were observed at any dose). ChE NOEL = 50 ppm (a decrease in whole blood ChE was observed in both sexes at 250 ppm--transitory in females and variable in males--at most 46.1% in Males and 54.5% in females, but these were inconsistent). ChE NOAEL > 250 ppm (levels of ChE inhibition observed in this study would not compromise the health of the animals). These data are considered supplementary. (The duplicate study 060 067245 was reviewed by B. Davis, 11/2/88 and prepared as a 1-liner in the SUMMARY OF TOXICOLOGY DATA--no worksheet. (Complete review and worksheet by M. Silva, 7/12/90).

#### Chronic Studies:

**046-48, 037034-7 (With rebuttal in 054, 052082):** "NC 6897 Toxicity and Tumorigenicity to Rats in Long-term Dietary Administration - Final Report Reproduction Phase and Main Phase," (Hunter, B., et al., Huntingdon Research Centre, 2/18/81). Bendiocarb (98.5% pure), was fed to CFY (Sprague-Dawley descended) rats, 100/sex/control or 50/sex/level for 2 years starting in utero at 200, 20, 10 (increased from 2 ppm at 4-6 weeks of age), or 0 p pm. **Possible adverse effect:** posterior cortical ocular opacities, NOEL = 20 ppm; cholinesterase inhibition, about 40% in blood and 25% in brain, both at 200 ppm, ChE NOEL 20 ppm. **NO ONCO EFFECTS** were observed. Originally reviewed as unacceptable no dose justification and incomplete diet analysis (Remsen [Gee], 12/10/85). Rebuttal does not change status, still UNACCEPTABLE: no MTD or adequate dose justification. Based on feed analysis, NOEL = 6 ppm, equivalent to 0.20 or 0.25 mg/kg/day for Males or females, respectively. Reproductive results reviewed separately. Martz, 9/29/87. Second rebuttal still does not change status. (Davis, 11/17/88).

50094-069 (pages only, no record number) Information was submitted to justify dose selection for 046-48, 037034-7, the eye effects, however, were not addressed. There was no change in status for the definitive study. (M. Silva, 7/13/90).

EPA One-liner: ACHE NOEL=20 ppm, interim report; no one-liner in Branch library for final

report.

038, 002322: One-page summary of #037034 above. (Gee , 6/17/85).

040, 017054: Text of #037034 above but without data. (Gee, 6/17/85).

054, 052082: Duplicate of #037037, which are feed analysis data for combined study.

054, 060: Rebuttals. (Martz 11/23/87, Davis 11/17/88).

066 In a rebuttal letter dated June 30, 1989, Nor-Am Chemical Company told of plans to initiate a subchronic dose range finding study. When the study is concluded, they will evaluate whether rats in a new rat combined study could be dosed high enough to warrant further testing. The results should be available in early 1990. This is not a commitment for further testing, however Nor-Am will contact CDPR to report their intentions when the tests are completed. (M. Silva, 8/4/89).

069 092516 "Technical Bendiocarb: Rat 15 Day Oral (Dietary) Range-Finding Study," (Schering Agrochemicals LTD., no date). Technical bendiocarb (CR 19306/1) was fed in diet to 5 male rats/dose (strain not specified) at 0, 200, 400, 800 and 1600 ppm (equivalent to 0, 22, 42, 84 or 161 mg/kg/day) for 15 days. NOEL < 200 ppm (depression of plasma acetylcholinesterase: 77%, 81%, 75% and 58% and brain cholinesterase: 55%, 55%, 41% and 39% at 200, 400, 800 and 1600 ppm respectively; 4/5 animals showed reduced muscle tone on day 14 at  $\geq$  800 ppm--piloerection was also shown at 1600 ppm). No adverse effect indicated. These data are supplementary. A summary only was submitted and the full study has been requested (NO WORKSHEET). (M. Silva, 5/23/90).

The rebuttal document (dated May 10, 1990) was accompanied by a letter (no volume or record number) with EPA evaluations of three mutagenicity and genetic toxicity studies which have also been evaluated at CDPR. The studies are listed below:

#### GENE MUTATION:

060 066152 "Technical Bendiocarb: Ames Bacterial Mutagenicity Test," (Huntingdon Research Centre, 7/16/87). No adverse effect. Acceptable.

#### CHROMOSOME EFFECTS:

**066 075266** "T348 Technical Bendiocarb: Metaphase Chromosome Analysis of Human Lymphocytes Cultured *in vitro*," (Huntingdon Research Centre, 6/13/88). **Possible adverse effect.** ACCEPTABLE.

#### DNA DAMAGE:

066 075268 "Technical Bendiocarb: Unscheduled DNA Synthesis in Cultured Mammalian Cell," (Huntingdon Research Centre, 10/31/88). No adverse effect. ACCEPTABLE.

This information was to be considered in our evaluation of the rat combined and reproduction studies. (M. Silva, 5/23/90).

#### CHRONIC, DOG

**\*\* 045, 037032:** "NC 6897 Toxicity Study in Beagle Dogs, Final Report: Dietary Intake for 104 Weeks," Huntingdon Research Centre, 3/24/80; Bendiocarb, 98-99% pure, was fed to Beagles, 8/sex/group, at 0, 20, 100 or 500 ppm in the diet for 2 years, with sacrifice 3/sex/group at 52 weeks. No Adverse Effects; NOEL=100 ppm, depression of whole blood and brain ChE at 500 ppm. ACCEPTABLE. (Gee, 12/9/85).

EPA One-liner: None in Branch library for final report; interim report - water consumption increasing in growth, 100 ppm, NOEL for blood CHE=100 ppm, HDT cholinesterase = 87% control (brain).

038, 002323: Three paragraph summary of #37032 above. Gee, 6/14/85.

040, 017053: Summary, table of contents, and methods of #37032 above but with no report or data. (Gee, 6/18/85).

#### ONCOGENICITY, MOUSE

\*\*049, 037038-9 (With rebuttal and supplemental information in -054, 052083 Tabs 2-4): "A Chronic Toxicity and Carcinogenicity Study in Mice NC 6897, Final Report." Hazleton (VA), 12/28/80; bendiocarb technical 92.7% purity, was fed to CD-1 mice, at 0 (100/sex), 50, 250 or 1250 (50/sex) ppm in the diet for 89 (males) or 94 (females) weeks. **Chronic effect:** increased absolute and relative testes and kidney weights at 1250 ppm, not regarded as adverse in absence of microscopic, lesions; Chronic NOEL = 200 ppm, corrected for analytical results. F. Martz, 10/11/87. No onco effect. Originally unacceptable - poor AI/feed concentration uniformity at low dose, no justification of dose levels with no clinical evidence of MTD, and test article contamination with 0.5% dimethoate, (Gee, 12/12/85). ACCEPTABLE based on the rebuttal of 5/4/88 (Record 067250) which justifies the high dose level by the Margin of Safety as suggested by Medical Toxicology, as well as the lack of any evidence for oncogenicity in any chronic studies. (Davis, 11/17/88).

EPA One-liner: Oncogenic NOEL>1250 ppm (HDT), interim report only.

038, 002321: Half-page summary of #037038 above.

040, 017055: Text of #037038 above but without data.

054, 060 067250: Rebuttals. (Martz 11/23/87, Davis 11/17/88).

#### SUPPORTIVE INFORMATION - MOUSE ONCOGENICITY

054, 052083 (Tab 2): "The effect of dietary administration of NC 6897 at 500 and 1000 ppm on whole blood cholinesterase activity in male mice of the CFLP and CD-1 strains;" FBC, 3/2/81; "unformulated" bendiocarb via the feed to CD-1 mice at 1000 or 500 ppm for 7 days; one subgroup sampled after continuous feeding, another sampled following 1 hour feeding after overnight fast; cholinesterase depression greatest (32%) in 500 ppm continuous feeding group, 5% in others. Results do not support use of 1250 ppm in mouse oncogenicity study (-049, 037038). No separate worksheet. (F. Martz, 11/9/87).

054, 052083 (Tab 3): "Determination of Bendiocarb (NC 6897) Dietary Concentrations in a Chronic Toxicity and Carcinogenicity Study in Mice;" Fisons, 6/80; Duplicate of 037039 in -049; contains feed analysis results showing intermediate dose blends (200 ppm) contained an average AI content of 80% of intent; necessitates reduction of nominal NOEL from 250 ppm to an actual NOEL of 200 ppm. No separate worksheet. (F. Martz 9/30/87).

054, 052083 (Tab 4): "A Comparison of the Acute Oral Toxicities of Various Batches of Bendiocarb CR 4971/2, CR 4799/9, CR 4799/4, and CR 4500/20 to the Male Rat, " Fisons, 5/80; oral LD<sub>50</sub> values as well as ED<sub>50</sub> values for clinical signs were similar between several batches of bendiocarb, one of which contained contaminants comparable to material used in mouse oncogenicity study (record #037038); similarity of values demonstrates unimpaired gastrointestinal absorption of AI in presence of contaminants, a criticism of the mouse oncogenicity study. Supplemental information answers CDPR criticism regarding

contaminants. No separate worksheet. (F. Martz, 9/30/87).

## REPRODUCTION, RAT

050, **037040-41 (With rebuttal in -054)**: "Technical NC 6897: Effects of Dietary Administration Upon Reproductive Performance and Teratogenic Response of Rats Treated Continuously Throughout 3 Successive Generations;" Life Science Research, 3/81; technical bendiocarb, 98%, in the feed at 250, 50, 10, or 0 ppm to 30/sex/group for 3 generations, 2 litters/generation, skeletal/Visceral exam of 112 of Flb, 2b, 3b; Maternal Effects: none; **Reproductive effects**: decreased birth weights and postnatal growth at 250 ppm; **Chronic effects**: trend for increased thyroid weight at 250 ppm without histopathologic changes, not an adverse effect. Originally, reviewed as UNACCEPTABLE: no MTD, with adverse reproductive effects (J. GEE, 6/18/85 and 12/13/85); reconsideration removes adverse effects except reduced peri/ postnatal growth, but rebuttal does not upgrade study, still UNACCEPTABLE and not upgradeable - no MTD. NOEL=50 ppm (reproductive and chronic). (F. Martz, 11/19/87).

EPA one-liner: Interim report only, NOEL = 50 ppm (1<sup>st</sup> generation); NOEL =10 ppm (2<sup>nd</sup> generation); depression in offspring body wt. (250 ppm); reduction of fertility (250 ppm); incomplete ossification vertebrae (250 ppm); no pathology data.

026, 992161: Interim report of #37040.

038, 002321: One-half page summary of #37040 above.

040, 017061: Incomplete report text of #37040 without data.

054, 060, 069 092516: Rebuttals. Martz 11/23/87, Davis 11/17/88, Silva 7/13/90, "Technical Bendiocarb: Rat 15 Day Oral (Dietary) Range Finding Study," (Schering Agrochemicals LTD., Summary only, no worksheet.)

**COMMENT:** Similar adverse effects have been observed in several studies conducted to assess various phases of the reproductive process. In the 3 generation study (#037040), birth weights were reduced as was the postnatal weight gain of the offspring at 250 ppm (HDT) in all 6 litters. Survival was reduced at 250 ppm, but in 2/6 litters only, discounting a treatment-relationship. Decreased postnatal weight gain and survival also occurred at 200 ppm (HDT) in the combined rat study which began exposure of its animals *in utero* (#037034, see below). A summary report of a "Segment III" type study noted reduced weight gain and increased mortality of pups in the 800 ppm group (HDT; #002317). Another summary of an *in utero* mortality study reported a slight trend for decreased fetal weight in Cesarean delivered offspring, but didn't specify the dose level at which this occurred (800 ppm=HDT; #002299). In view of the reproducibility of effects occurring under a variety of conditions, an acceptable definitive study is necessary. Martz, 11/30/87. A summary of a pilot study was submitted in a rebuttal dated May 10, 1990 (069 092516: "Technical Bendiocarb: Rat 15 Day Oral (Dietary) Range Finding Study," (Schering Agrochemicals LTD.) to justify the dose range selected for the rat reproduction study. It was stated that 250 ppm was acceptable for the high dose because plasma and brain cholinesterase values did not significantly change at > 200 ppm (see below):

Dose	Reduction in Cholinesterase Values (%) Compared to Controls	
	Brain	Plasma
0	100	100
200	77	55

400	81	55
800	75	41
1600	58	39

Based upon the data presented, CDPR does not agree with this evaluation. At 1600 ppm both plasma and brain ChE continue to decrease and in addition, some clinical signs (reduced food consumption and reduced muscle tone at  $\geq 800$  ppm with piloerection observed at 1600 ppm), were noted. Therefore, 250 ppm is not an acceptable high dose for the rat reproduction study. (M. Silva, 7/17/90).

#### MISCELLANEOUS REPRODUCTION INFORMATION

038, 002299: Three paragraph summary of *in utero* mortality study; bendiocarb at 800, 400, 200, or 0 ppm in the feed to males and females 1 week pre-mating through gestation day 19 with necropsy on day 21; slight delay in mating at 800 ppm, slight trend for decreased fetal weight (dose?), no other reproductive effects or clinical signs reported. (Gee, 6/17/85 and Martz, 11/17/87).

038, 002317: Three paragraph summary of "Segment III" type study; bendiocarb in the feed at 800, 400, 200, or 0 ppm, gestation day 14 until weaning; decreased maternal and pup weight gain and increased pup mortality at 800 ppm, with "morphological abnormalities," NOEL=400 ppm. (Gee, 6/17/85 and Martz, 11/17/87).

EPA One-liner: Decreased body weight in both parents and pups at HDT (800 ppm).

038, 002319: Two paragraph summary of estrus cycle study; bendiocarb in the feed at 800, 600, 400, 0 ppm for 28 days; clinical signs of cholinesterase inhibition at 800 ppm and 600 ppm only after 1 hour feeding period following overnight fast; no other effects reported. (Gee, 6/17/85 and F. Martz, 11/17/87).

**046, 037034:** "Toxicity and Tumorigenicity to Rats in Long-term Dietary Administration - Final Report - Reproduction Phase and Main Phase" - one litter, one generation, F<sub>1</sub> used for combined study; Huntingdon Research Centre, 2/18/81; Bendiocarb, 98.5%, was fed to CFY (Sprague-Dawley descended) rats, F<sub>0</sub>: 30 males-60 females/200, 20, or 2 ppm; 60 males-120 females/0 ppm; **Adverse Effects** - @ 200 ppm, decreased pup survival mostly days 0-4, and reduced postnatal weight gain; study not applicable for reproduction data requirement, but has scientific merit. Combined study reviewed separately. (Martz, 10/6/87).

EPA One-liner: Interim report only, no effect on reproduction performance, increased mortality from day 0 to day 4 at HDT.

040, 017054: Summary of #037304 above with no data presented. (Gee, 6/17/85).

066 In a rebuttal letter dated June 30, 1989, Nor-Am Chemical Company told of plans to initiate a subchronic dose range finding study. When the study is concluded, they will evaluate whether rats in a new reproduction study could be dosed high enough to warrant further testing. The results should be available in early 1990. This is not a commitment for further testing, however Nor-Am will contact CDFA to report their intentions when the tests are completed. (M. Silva, 8/4/89).

076 089936, "Technical Bendiocarb: Rat Oral Developmental Toxicity (Teratogenicity) Study", (A.I. Brooker, C. Brennan and D.M. John, Huntingdon Research Centre Ltd., HRC Study No.: SMS 206/901691, 7/15/91). Technical Bendiocarb, purity 91.2% was administered by intragastric intubation at concentrations of 0 (1% methylcellulose), 0.4, 2.0 or 10 mg/kg/day to 25-30 mated female Crl: CD<sup>®</sup> (SD) BR VAF/Plus rats/group during days 6 through 15 of gestation. Treatment related effects included increased incidence of lip smacking, muscle twitching, body tremors and salivation; also, slightly reduced body weight, increased water intake and decreased food consumption for the high dose maternal group. Maternal NOEL = 2.0 mg/kg/day (Clinical signs, slight decrease in body weight gain). Embryonic deaths increased for the high dose group. Developmental NOEL = 2.0 mg/kg/day. UNACCEPTABLE. Upgradeable. Study did not report on dosing solution analysis. (Kishiyama and Gee, 4/3/97).

003, 992159: "The Teratogenicity of NC 6897 to the Rat;" Fisons Ltd., 1174; bendiocarb technical, no purity stated, dissolved in propylene glycol, administered by gavage on days 6-15 of pregnancy (positive vaginal smear Day 0 at 0, 0.25, 1.0, or 4.0 mg/kg/day (dose volume = 1 ml/kg) to 25 CD females/level (16 to 23/level pregnant at necropsy). Maternal Effects: clinical signs of cholinesterase inhibition at 4 mg/kg; Developmental Effects increased resorptions at 4 mg/kg; No malformations; maternal NOEL = developmental NOEL = 1 mg/kg/day. UNACCEPTABLE: no test article analysis, fetal fixation difficulties, no individual bodyweights or gross pathology of dams, and fetuses not sexed. (Gee, 6/13/85).

054, 052084: Exact duplicate of #992159.

**054, 052085;** "Teratogenicity Study in the Rat" (Consultox Laboratories Ltd., 4/74). Bendiocarb, 97%, (in 0.5% tragacanth) at 0, 0.25, 1 or 4 mg/kg by gavage to 21-22 pregnant CD rats/level, days 6-15 of gestation (plug=day 0); Maternal effects: decreased body weight gain and signs of ChE inhibition at 4 mg/kg, NOEL=L mg/kg/day; **Adverse developmental effect:** late intrauterine death, NOEL<0.25 mg/kg/day. UNACCEPTABLE and not upgradeable: inadequate skeletal examinations, no dosing suspension analysis. NOEL<0.25 mg/kg/day (fetotoxicity). (D.A. Shimer, and F. Martz, 11/20/87).

EPA One-liner: Mild cholinergic signs at the 4 mg/kg (HDT); terata NOEL>4 mg/kg (HDT); unclear whether refers to #052085 or #992159.

0384 031117: Two paragraph summary of #052085 or 992159 (can't tell). (Gee, 6/17/85).

050, 037040-41 (With rebuttal in 054): "Technical NC 6897: Effects of Dietary Administration Upon Reproductive Performance and Teratogenic Response of Rats Treated Continuously Throughout 3 Successive Generations;" Life Science Research, 3/81; technical bendiocarb, 98%, in the feed at 250, 50, 10, or 0 ppm to 30/sex/group for 3 generations, 2 litters/generation, skeletal/visceral exam of 112 of F1b, 2b, 3b; Maternal effects: none; Developmental effects: none. Originally reviewed UNACCEPTABLE no MTD, with "subcutaneous space over cranium" as adverse effect (Gee, 6/18/85 and 12/13/85); reconsideration removes adverse effect but rebuttal does not upgrade study, still UNACCEPTABLE and not upgradeable: no MTD. NOEL>250 ppm (Maternal and developmental. ( Martz, 11/18/87).

EPA One-liner: Interim report only, incomplete ossification vertebrae (250 ppm). EPA Reregistration Standard of 1987 considers this study to be inadequate.

026, 992161: Interim report of #37040 above. (Gee, 6/13/85). -

031, 031075: Report and tables of #37040 but without appendices. (Gee, 6/14/85).

040, 017061: Incomplete report text of #037040 without data.

054, 060: Rebuttals. (Martz 11123187, Davis 11/17/88).

**Conclusion:** Two studies (Record 992159 = T39 & Record 052085 = T43) provide evidence for increased resorptions. The third study (Record 037040-41) found neither maternal nor developmental toxicity, and an MTD was not reached. Lower toxic effects may have been observed in this latter study because bendiocarb was administered by diet, rather than by gavage. It is difficult to accurately compare test results when different routes of administration are used. Because of the inconsistency in the results a NOEL cannot be set. Therefore, the data gap is not filled but there is evidence of an adverse developmental effect (Davis, 11/17/88. M. Silva, 8/4/89). Revision: Review of a more recent study, # 089936 in 50094-076, supports a Maternal NOAEL and Developmental NOEL of 2 mg/kg body weight/day. This is in agreement with 2 of the 3 studies above. The weight-of-evidence indicates no specific developmental effects in the absence of maternal clinical signs. (Gee, 4/3/97).

066 A rebuttal letter dated June 3, 1989, contained a discussion to justify the acceptability of the rat teratology study. (Silva, 8/4/89).

069 092516 This rebuttal document contained a commitment for a new rat teratology study, to be completed by January, 1991. [See -076, 89936].

#### TERATOLOGY, RABBIT

\*\* 051, 037046 (with rebuttal and supplemental information in -054, 052086): "Technical NC 6897: Effects of oral administration upon pregnancy in the rabbit (5) Definitive study;" LSR, 12/29/80; technical bendiocarb, 99%, by gavage in 0.5% gum tragacanth at 5, 2.5, 1 or 0 mg/kg/day to 27-29 level on gestation days 6-28 (insem=day 0); Maternal Toxicity: clinical signs of cholinesterase inhibition, pronounced cholinesterase inhibition, reduced weight gain, NOEL= 1 mg/kg/day; No developmental toxicity, NOEL>5 mg/kg/day(HDT); unacceptable in prior review (Parker, 12/16/85) - no clinical observations or scheduled necropsy observations; rebuttal with clinical observations (52086) upgrades study to Complete and ACCEPTABLE. (Martz, 11/10/87).

EPA One-liner: None in Branch library. According to the EPA Reregistration Standard of 1987, no additional data are required. (M. Silva, 7/17/90).

038, 031118: Half-page summary of #37046 above. (Gee 6/17/85).

#### MISCELLANEOUS RABBIT STUDIES

Four studies (037042-45) conducted prior to the "Definitive Study" above were as follows:

051, 037042: "Technical NC 6897: Effects of oral administration upon pregnancy in the rabbit. 1. Dosage range-finding study" (initiated 8/2/79); LSR, 1/24/80; technical bendiocarb (purity unspecified) by gavage in 0.5% gum tragacanth at 20, 10, 5, 2.5, or 0 mg/kg to 4 level on gestation days 6-28 (insem=day 0); **Maternal toxicity:** mortality at 20 mg/kg, dose-related clinical signs; **Developmental effects:** fetal and placental weight differences inconclusive, no gross or internal fetal abnormalities; 10 mg/kg recommended as top dose level for main study. No separate worksheet. (Martz, 11/10/87).

051, 037043: "Technical NC 6897: Effects of oral administration upon pregnancy in



the rabbit (2) Main study" (initiated 12/6/79); LSR, 8/12/80; technical bendiocarb, 99%, by gavage in 0.5% gum tragacanth at 10, 5, 2.5, or 0 mg/kg to 14-16/level on gestation days 6-28 (insem=day 0); Maternal toxicity: at 10 mg/kg, 1 death and severe clinical signs, with lesser signs at 5 mg/kg, dose-related body weight effects, NOEL<2.5 mg/kg/day (body weight); Developmental effects: gross cranial anomalies and reduced fetal and placental weights at 10 mg/kg only, inconclusive increase in gall bladder variants, NOEL=5 mg/kg, further studies recommended. No separate worksheet. (F. Martz 11/10/87).

051, 037044: "Technical NC 6897: Effects of oral administration upon pregnancy in the rabbit (3) Interim study" (initiated 2/25/80); LSR, 8/12/80; technical bendiocarb, 99% pure, by gavage in 0.5% gum tragacanth at 10 mg/kg to 25 on gestation days 6-28 (insem=day 0); **Maternal toxicity:** mortality, clinical signs, abortion, weight loss and reduced gain; Developmental toxicity: 3 fetuses with multiple malformations grossly, these plus several others with skeletal anomalies, further studies recommended. No separate worksheet. (Martz, 11/10/87)

051, 037045: "Technical NC 6897: Effects of oral administration upon pregnancy in the rabbit (4) Preliminary study of cholinesterase activity" (initiated 4/29/80); LSR, 8/13/80; technical bendiocarb, 99%, by gavage in 0.5% gum tragacanth 5 or 0 mg/kg to 3/level on gestation day 20 with separate 3/level on day 24 (insem=day 0) with cholinesterase assay 30 minutes postdose and necropsy day 29; Maternal toxicity: clinical signs, weight loss and reduced gain, CHE depressed to 48% of control on day 20 (no pretest assay), and on day 24 to 39% of control or 32% of pretest values; Developmental toxicity: none indicated, but group size limited, final definitive study indicated. No separate worksheet, (Martz, 11/10/87).

051, 037047: "Evaluation of the spontaneous incidence of a cranial abnormality compared with NC 6897 treated animals; "historical control data for craniofacial anomalies at LSR. No separate worksheet. (Martz, 11/10/87).

051, 037048: "Determination of bendiocarb (NC 6897) concentrations in aqueous gum tragacanth suspensions for a teratology study with rabbits;" dosing solution analysis results for "Main Study," record #37043, indicate homogeneity and stability under use conditions, and ability to prepare intended concentrations. Results support "Definitive Study," record #37046, in which dosing solution analysis was not done. No separate worksheet. (Martz, 11/10/87).

040, 017060: Summary of #37042-46 above. (Gee, 6/18/85).

Comment: While only the fifth study in the series of 5 (37046 vs 37042-45) is acceptable to fill a specific data requirement, the other 4, taken as a whole, are exemplary regarding design, conduct and reporting, and reinforce the lack of teratogenic potential in the absence of severe maternal toxicity in rabbits. (Martz, 11/10/87).

## GENE MUTATION

\*\* 040, 037051: "Microbial Mutagenicity Study of Bendiocarb (KNT)," (Reverse Mutation test with *E. coli* and *S. typhimurium*; Institute of Environmental Toxicology (Tokyo), 8/5/81); Bendiocarb, 98.8%, was tested with *E. coli* and *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100 and *E. coli* WP2hcr at 7 concentrations from 5 to 5000 ug/plate; +/- activation. **No increase** in revertants. ACCEPTABLE. (Gee, 6/19/85).

\*\*060 066152 "Technical Bendiocarb: Ames Bacterial Mutagenicity Test" (Huntingdon Research Centre, T346, 7/16/87) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, in triplicate plates, exposed to technical bendiocarb (CR 20859/1, 100%

w/w) at 0, 15, 50, 150, 500, 1500 ug/plate with and without activation, 72 hours at 37° C; two assays. NO ADVERSE EFFECT; ACCEPTABLE. (Davis 11/17/88).

040, 017056: "Testing the Mutagenic Activity of Technical NC6897;11 Inveresk Research International, 6/79; Technical bendiocarb was tested with *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 at 8 concentrations from 3.3 µg/plate to 10 mg/plate; +/- activation. UNACCEPTABLE. Poor response with positive control in TA1535 and TA1537. (Gee, 6/19/85).

038, 002315: Two paragraph summary of 017056 or 037051. (Gee, 6/17/85).

060: Nor-Am rebuttal agrees that the study (017056) had a poor response with the positive control agent and proposes to withdraw it.

### CHROMOSOME EFFECTS

**\*\* 066 075266** "T348 Technical Bendiocarb: Metaphase chromosome analysis of human lymphocytes cultured *in vitro*," (Huntingdon Research Centre, 6/13/88). Technical Bendiocarb (BatZ-h CR 20859/2, 97.6%) was used on human lymphocytes at 0 (DMSO), 14.3, 71.5 and 143 ug/ml (without metabolic activation) or 30, 150, 225 and 300 ug/ml (with activation). Cells with S-9 were exposed to bendiocarb for 2 hours and cells without S-9 were exposed for 24 hours and both groups were sampled 24 hours after treatment. No effects were observed in the absence of metabolic activation. Positive controls functioned as expected. **An adverse effect**, seen as an increased incidence of chromosomal aberrations, was noted at ≥150 ug/ml when metabolic activation was used. The study is complete and ACCEPTABLE. (M. Silva, 7/31/89).

**\*\* 066 075267** "T353 Technical Bendiocarb: Analysis of Metaphase Chromosome From Rat Bone Marrow," (Huntingdon Research Centre, 1/3/89). Bendiocarb technical (Batch #: CR 20859/2, 97.6% pure) was administered to CrI:CD (SD) BR rats at 0 (vehicle = 1% w/v methylcellulose in distilled water), 2.6, 13 or 26 mg/kg by gastric intubation. A positive control was treated with cyclophosphamide by intraperitoneal injection at 40 mg/kg bodyweight. Animals were terminated at 6, 24 and 48 hours (5/sex/group) and positive controls were killed 24 hours after treatment. The number of metaphase spreads scored/animal = 50. Mortality was: 0/5 for 0, 2.6, 13 mg/kg and 6/11 (males) or 3/8 (females) for 26 mg/kg at 6 hours; at 24 & 48 hours, 0/10 for vehicle control, 0/12 at 2.6 mg/kg, 1/12 (males) and 0/12 (females) for 13 mg/kg and 5/14 (males) or 5/17 (females) at 26 mg/kg. The positive control showed 0/5 at 48 hours. There was no increase in chromosome damage in any of the groups treated with bendiocarb. The positive control functioned as expected. ACCEPTABLE. (M. Silva, 8/1/89).

051, 037049 (With rebuttal and supplemental information in -054, 051359): "A Test for the Induction of Dominant Lethal Mutations in Male Rats by NC6897;" Fisons Ltd, 4/77; technical bendiocarb in the feed to Sprague Dawley male rats, 20/group, at 0, 10, 50 or 250 ppm for 13 weeks. Males were then mated for 1 week with 1 or 2 females. No effects or clinical signs are reported. NOEL > 250 ppm. Originally reviewed (Gee, 12/9/85) as UNACCEPTABLE: Dose too low, unusual treatment schedule with no justification, insufficient females, no feed analysis; Not upgraded by rebuttal, still UNACCEPTABLE, not upgradeable, same reasons. (Gee, 8/4/87).

038, 002316: Two paragraph summary of #037049.

051, 037053 "A Micronucleus Study in Mice Using Technical NC6897 CR4971/2." (FBC Limited) CD-1 mice given two i.p. injections, 24 hours apart at 0, 0.625, 1.25 or 2.5 mg/kg in

propylene glycol, 5/males/group. Animals were sacrificed 6 hours after the 2nd injection. UNACCEPTABLE. Should also use females. (Gee, 6-19-85).

040, 017058: Text of #037053 above but without data.

**Conclusion:** The test using human lymphocytes (075266) demonstrated an adverse effect, where the *in vitro* bioassay (075267) with rats did not. The weight of evidence for adverse effects would tend to consider effects observed in human cells as more significant than effects in other mammalian cells *in vitro*. Other tests performed in this series, such as the dominant lethal test (037049), and the micronucleus test in mice (037053) were negative. The dominant lethal and micronucleus tests assess different end-points than the chromosome aberration test, and thus are not directly comparable. Therefore, an adverse effect is indicated for Bendiocarb on the DNA of human lymphocytes. (M. Silva, 8/4/89). (Revised by Gee, 4/3/97)

#### DNA DAMAGE/REPAIR

**\*\*066 075268** "Technical Bendiocarb: Unscheduled DNA Synthesis in Cultured Mammalian Cells," (Huntingdon Research Centre LTD., 10/31/88). Technical Bendiocarb (Batch #: CR 20859/2, 97.6% pure) was used on HeLa S3 epithelioid cells in monolayer cultures with and without S-9, in duplicate cultures at 0 (vehicle = DMSO), 1.25, 2.50, 5, 10, 20, 40, 80, 160, 320, 640, 1280, 2560 ug/ml (ppt. formed at highest concentration) for 180 minutes. Tests with and without S-9 were repeated. No significant effects were observed at any dose. Positive controls performed as expected. ACCEPTABLE. (M. Silva, 8/1/89).

**051, 037054 (with rebuttal in -054)** "Technical Bendiocarb: Induction of Gene Conversion and Mitotic Recombination in Yeast;" Inveresk, 8/2/82; technical bendiocarb, 98.5, was tested with *Saccharomyces cerevisiae* D7 for gene conversion and mitotic recombination at 0 - 6 mg/ml for 18 hours with and without Aroclor induced rat liver activation, positive controls EMS and CPAM. **Possible increased mitotic recombination.** Prior review (Gee, 6/18/85 and 12/9/85), UNACCEPTABLE: report incomplete and positive control with S9 of questionable response, not upgraded by either rebuttal (Martz 11/30/87, Davis 11/17/88). Main review Gee, 8/6/87.

040, 017059: Text of #37054 above but with no data. (Gee, 6/18/85).

060, 066293: Excerpts from 037054. (Davis, 11/17/88).

040, 017057: "The Microbial Mutagenicity Study of Bendiocarb;" Institute of Environmental Toxicology, 8/81; bendiocarb, 98.8% was tested with *B. subtilis* strains H17 and M45 at 8 concentrations from 20 to 5000 ug/disk. UNACCEPTABLE. Lack of repeat experiment and replicate values. No cytotoxicity at any concentration = no test. (Gee, 6/19/85).

038, 002314: One paragraph summary of #017057.

060, 066274: Identical with 017057.

**Conclusion:** All tests in this category measure different end-points and are not comparable. In addition, the test in *B. subtilis* showed no cytotoxicity at the highest concentration and is, therefore, considered a no-test. In the study with yeast, an adverse effect was noted, however in the most recent test, performed in human Hela cells, no adverse effect was observed. The weight of evidence would favor the results where human cells are utilized, therefore, Bendiocarb does not demonstrate an adverse effect for DNA damage. (M.Silva, 8/4/89).

## NEUROTOXICITY

001, 992154: "Toxicology of NC6897. Test for Neurotoxicity of NC 6897 to the Chicken;" Fisons Limited, 11/69; Bendiocarb, no purity stated, by subcutaneous injection at 60 mg/kg ( $LD_{50}$  = 80 mg/kg) to Rhode Island Red hens, 7/group, 2 doses 3 weeks apart. UNACCEPTABLE. Unprotected dose, no effects were reported. (Gee, 6/17/85).

EPA One-liner: NOEL=60 mg/kg (75%  $LD_{50}$ ).

038, 002313: Two paragraph summary of #992154 above. (Gee, 6/17/85).

026, 992137: "Examination of NC6897 for Neurotoxicity in Domestic Hen;" Huntingdon Research Centre, 10/78; Technical bendiocarb given in a single dose by gavage to atropine protected hens, 20 at 757, 10/level at 378, 189, or 0 mg/kg, or TOCP positive control ( $LD_{50}$  = 137 mg/kg without atropine, 757 mg/kg with atropine); No adverse effect at  $LD_{50}$ ; UNACCEPTABLE. Hens not redosed after 21 days, no analysis of test agent, no ataxia in hens treated with atropine. (Gee, 6/13/85).

EPA One-liner: Not neurotoxic, NOEL = 757 mg/kg (HDT) with atropine protection at mg/kg.

038, 002298: Two paragraph summary of #992137. (Gee, 6/17/85).

COMMENT: While none of these studies are acceptable, delayed neurotoxicity testing is not required for carbamate type insecticides at this time.